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Original Article

Efficacy and tolerability of a new nasal spray formulation containing hyaluronate and tobramycin in cystic fibrosis patients with bacterial rhinosinusitis

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Abstract

Background: Chronic rhinosinusitis is common in cystic fibrosis (CF), as CFTR defects equally affect the airway and sinonasal mucosa. However, therapeutic strategies for CF-associated chronic rhinosinusitis lag behind current approaches for pulmonary disease.
Objective: To assess the tolerability and efficacy of a nasal spray formulation containing 0.2% sodium hyaluronate and 3% tobramycin compared to a control formulation containing 0.2% sodium hyaluronate alone in the treatment of bacterial rhinosinusitis in patients with CF.
Methods: In a double-blind controlled study, 27 patients with an established diagnosis of CF and a documented nasal infection with *Pseudomonas aeruginosa* and/or *Staphylococcus aureus* [22 males (81%), median age of 15 years (range 5–26 yrs)], were randomized to receive the nasal spray formulation containing hyaluronate and tobramycin ($N = 14$) or hyaluronate alone ($N = 13$) for 14 days. Efficacy and local tolerability of the treatments were assessed by ear, nose and throat (ENT) examination and related symptoms.
Results: The formulation containing hyaluronate and tobramycin was more effective than hyaluronate alone in improving the status of the nasal mucosa, in reducing the mucopurulent secretion at the level of the osteomeatal complex and in improving ENT symptoms (hyposmia/anosmia and headache/facial pain). The treatment was well tolerated without relevant side effects.
Conclusions: The present study suggests that the combination therapy with hyaluronate plus tobramycin was more effective than hyaluronate alone in the treatment of bacterial rhinosinusitis in CF. Trial registration number: EudraCT 2007-003628-39.

Keywords: Cystic fibrosis; Bacterial rhinosinusitis; Nasal spray formulation; Hyaluronic acid; Tobramycin

1. Introduction

Chronic rhinosinusitis is very common in cystic fibrosis (CF), being reported in 30–67% of affected patients over all age groups [1,2], with classic and atypical form of the disease [3]. It is associated with a wide spectrum of clinical symptoms (including nasal obstruction, impaired olfactive function and facial pain) that have a significant impact on quality of life [4].

Recently, the influence of the upper airways on the general health of CF patients has been the object of investigation to verify the hypothesis that sinonasal involvement may function as a reservoir for pulmonary infection. Several studies have documented concordance between microorganisms isolated in the upper and lower airways, supporting the unified airway

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concept and also the idea that colonization of the upper airways may precede spread to the lower airways [5–8].

In a group of 16 CF patients who underwent endonasal endoscopic sinus surgery, a significant association was found between bronchoalveolar lavages and sinus cultures [5]. More recently, a cross-sectional study in adult CF patients also comparing upper and lower cultures has shown one or more concordant microorganism in 50% of the patients [8]. *Pseudomonas aeruginosa* was frequently cultured from upper airways and this also occurred after eradication therapy.

Treatment strategies for CF-associated chronic rhinosinusitis vary but usually include a combination of endoscopic sinus surgery, systemic and topical antibiotics/steroids and nasal irrigations [9]. In consideration of the unified airway concept, other therapeutic interventions currently used for pulmonary disease provide potential benefits.

Hyaluronic acid (HA) has been shown to exert beneficial effects in experimental models of chronic respiratory diseases [10]. Due to its water-retaining properties, it humidifies and protects the respiratory airways against injury and is also provided of anti-inflammatory properties [11]. More recently, nebulized HA has been shown to be effective in controlling inflammation in vivo in mice CF airways and in vitro in human airway epithelial cells, thus providing the proof of concept for its use as a potential anti-inflammatory drug in CF therapy [12]. HA inhalation has also been shown to be effective and safe in CF patients with lung disease [13]. However, the inhalation of HA alone does not decrease bacterial load in these patients. Therefore, a nasal spray formulation of HA plus tobramycin was developed to provide the benefits of HA together with the bacteriostatic and bactericidal (at high concentration) effects of tobramycin.

In this study, we compared the efficacy and tolerability of this new formulation with a nasal spray formulation containing HA alone, in the treatment of bacterial rhinosinusitis in patients with CF.

2. Materials and methods

2.1. Study design

We carried out a randomized, double-blind controlled parallel-group pilot study aimed to test the tolerability and efficacy of a 2-week treatment of a nasal spray formulation containing 0.2% sodium hyaluronate and 3% tobramycin compared to a control formulation containing 0.2% sodium hyaluronate alone in CF-associated bacterial rhinosinusitis. The study was carried out at the CF Centre, Fondazione IRCSS, Ca' Granda Ospedale Maggiore Policlinico of Milan in compliance with the Declaration of Helsinki and the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice. The institutional ethics committee approved the study, and all patients or their guardians provided written informed consent prior to undergoing any study procedures. The trial registration number is EudraCT 2007-003628-39.

Patients older than 6 years with an established diagnosis of CF (sweat chloride >60 mEq/L and/or presence of two CF causing mutations), symptoms of rhinosinusitis and a forced expiratory volume in one second (FEV 1) of at least 30% of the predicted value were considered for the enrolment. Exclusion criteria were a history of hypersensitivity to aminoglycosides, a negative sinus culture for both *P. aeruginosa* and *Staphylococcus aureus*, pregnancy or breastfeeding and the use of systemic antibiotics within 30 days before enrolment in the study. Patients colonized by *Burkholderia cepacia* were also excluded because of the multidrug resistance of the bacterium. Finally, in consideration of the nasal route of administration, patients with deviation of nasal septum totally obstructing one nasal cavity or suffering from allergic rhinitis or sinonasal polyposis, those with ongoing or recurrent epistaxis or with a history of endoscopic sinus surgery in the 6 months preceding enrolment were excluded from the study.

During the study period, patients were allowed to take their usual treatments or to take drugs for any concomitant diseases. However, systemic antibiotic treatment or local nasal treatments with anti-inflammatory drugs were not allowed for the duration of the study.

In all eligible patients, swab cultures obtained from osteomeatal complex were taken under endoscopic control for the identification of pathogens (*P. aeruginosa* and/or *S. aureus* bacteria). We considered the middle meatus representative for the upper airways as a concordance of cultures obtained by middle meatal swab with maxillary sinus aspirate has been confirmed by a meta-analysis [14]. The nasal swabs were placed into 1 mL of 0.9% sodium chloride for processing. After 20 min, the samples were vortexed and 0.1 mL was cultured on different agar plates to detect Gram-positive and Gram-negative bacteria. All samples were incubated aerobically at 37 °C and were analysed for growth of bacteria after 18 h and then every 24 h during 7 consecutive days. Each microorganism isolated was identified by a standardized and automated method (Microscan System Siemens HD). A sputum culture was also performed at the same day visit. Enrolled patients were randomly assigned to one of the two treatment groups using a computer generated randomization code. The test nasal spray formulation consisted of a 10-mL aqueous solution containing 0.2% sodium hyaluronate (MW 0.3–0.5 Mda, obtained by fermentation from *Streptococcus equi* bacterial strain; CPN Spol Dolni Dobrouc 401, 561 02) and 3% tobramycin sulphate. The control nasal spray formulation was identical in presentation but contained only 0.2% sodium hyaluronate. The two test products were packed in identical containers. Each patient nebulized 100 μL of the assigned product into each nostril 3 times a day for 14 days.

The study participants, investigators and study monitors were blind to the treatment assigned to the patients. However, the investigator had access to a sealed envelope containing the randomisation code of each patient to be opened in case of a medical emergency. Data entry and data analysis were also performed in a blind manner, i.e., before the codes were broken.

At baseline (Visit 1, Day 1) and at the end of the study (Visit 2, Day 14), patients underwent nasal endoscopy using the 2.2 flexible optical scope from Olympus NF XP (Olympus

Corporation, Tokio, Japan) and were asked about ear, nose and throat (ENT) symptoms, including nasal obstruction, mucopurulent rhinorrhea, hyposmia/anosmia, snoring, headache and facial pain.

Local tolerability of the 2 formulations was assessed through ENT examination and occurrence of new symptoms (specifically dryness of the mucosa, bleeding and/or sneezing) and/or worsening of already present symptoms. Treatment was considered tolerable if the patients did not report worsening or occurrence of ENT symptoms and if the endoscopic evaluation did not show an alteration of the nasal mucosa.

At endoscopic evaluation, nasal mucosa was classified as eutrophic (healthy and well hydrated), hyperaemic (flushed with evident vascular ectasia) or dystrophic (dry, pale and atrophic). In addition, we evaluated the presence of mucopurulent secretions at the level of osteomeatal complex (suggestive for infectious/flogistic involvement of the anterior compartment of paranasal sinuses) and of hypertrophy of turbinates (particularly the lower, with consequent choanal obstruction and accumulation of secretions).

2.2. Statistical analysis

Study outcomes were as follows: changes in symptoms related to sinonasal infection, mucosal inflammation and reduction of bacterial load in nasal swab, expressed in colony forming unit (CFU)/mL. Changes in ENT symptoms and in signs of mucosal inflammation were categorized as follows: improvement (symptoms/signs present at baseline and absent at visit 2), worsening (symptoms/signs absent at baseline and present at visit 2) or no change (symptoms/signs absent at baseline and at visit 2 or symptom present at baseline and at visit 2).

Considering that for many outcomes the category "worsening" had an observed frequency equal to 0 and an expected frequency less than 5 we pooled the categories "worsening" and "no change" and performed the Fisher's exact test to verify if the proportions of patients in the categories of the outcome are independent of the treatment group.

As a secondary objective, we evaluated the association between upper airways and lower airways infections in all the screened patients. The odds of a positive sputum culture for *S. aureus* or *P. aeruginosa* in patients with a positive and negative sinus specimen were calculated. The odds ratios (ORs) and their 95% CIs were also computed.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS v. 15.0) and significance was set at $\alpha < 0.05$.

3. Results

Fifty-nine patients with symptoms suggestive of bacterial rhinosinusitis were screened but 32 were excluded: 20 patients had a negative sinus culture and 12 patients (10 with positive cultures for *S. aureus* and 2 for *P. Aeruginosa*) were not included because of systemic antibiotic treatment within 30 days before enrolment). Twenty-seven patients with a positive sinus swab culture (23 for *S. aureus,* 2 for *P. aeruginosa* and 2 for both bacteria) were enrolled in the study.

The enrolled patients were randomly assigned to receive the test formulation ($N = 14$) or the control formulation ($N = 13$) for 14 days. The baseline characteristics of the patients are shown in Table 1.

Patients were comparable for demographic and clinical characteristics, with the exception of a higher proportion of *P. aeruginosa*-positive cultures and a lower prevalence of continuous nasal obstruction in patients receiving HA and tobramycin (Table 1).

The presence of 3% tobramycin in the test formulation did not modify the already known tolerability of the 0.2% sodium hyaluronate control nasal formulation [15]. Both formulations were well tolerated; none of the patients reported significant worsening or occurrence of ENT symptoms including dryness, bleeding and/or sneezing.

The combination of HA and Tobramycin was more effective in reducing hyposmia/anosmia and headache/facial pain than HA alone, while no significant differences were found for other ENT symptoms (Table 2).

Table 1
Baseline characteristics of the patients.

	Hyaluronate ($N = 13$)	Hyaluronate + tobramycin ($N = 14$)
Gender (M/F)	10/3	12/2
Age, median (range)	15 (5–24)	16 (6–26)
Genotype		
Delta F508 homozygous, *n* (%)	3 (23%)	3 (21%)
Delta F508 heterozygous, *n* (%)	4 (31%)	6 (43%)
Others, *n* (%)	6 (46%)	5 (36%
Pancreatic insufficiency, *n* (%)	7 (54%)	8 (57%)
Positive *Pseudomonas aeruginosa*		
Sputum, *n* (%)	0	6 (43%)
Nasal swab, *n* (%)	0	4 (29%)
Positive *Staphylococcus aureus*		
Sputum, *n* (%)	8 (62%)	9 (64%)
Nasal swab, *n* (%)	13 (100%)	12 (86%)
FEV1 (% of the predicted value), median (range)	101 (50–120)	98 (36–127)
Symptoms		
Nasal obstruction		
Absent, *n* (%)	0	1 (7%)
Occasional, *n* (%)	5 (38%)	8 (57%)
Continuous, *n* (%)	8 (62%)	5 (36%)
Mucopurulent rhinorrhea (subjective evaluation), *n* (%)	12 (92%)	12 (86%)
Hyposmia/anosmia, *n* (%)	8 (62%)	12 (86%)
Snoring, *n* (%)	8 (62%)	9 (64%)
Headache/facial pain, *n* (%)	8 (62%)	12 (86%)
Endoscopic evaluation		
Nasal mucosa		
Eutrophic, *n* (%)	0	0
Hyperemic, *n* (%)	10 (77%)	11 (79%)
Dystrophic, *n* (%)	3 (23%)	3 (21%)
Mucopurulent secretion of osteomeatal complex, *n* (%)	12 (92%)	13 (93%)
Hypertrophy of the left turbinate, *n* (%)	10 (77%)	12 (86%)
Hypertrophy of the right turbinate, *n* (%)	11 (85%)	13 (93%)

Table 2
Changes in ENT symptoms.

	Hyaluronate (N = 13)	Hyaluronate + tobramycin (N = 14)	P-value
Nasal obstruction			
Improvement, *n* (%)	10 (77%)	9 (64%)	0.68
No change, *n* (%)	3 (23%)	5 (36%)	
Worsening, *n* (%)	0	0	
Mucopurulent rhinorrhea (subjective evaluation)			
Improvement, *n* (%)	7 (54%)	9 (64%)	0.70
No change, *n* (%)	6 (46%)	5 (36%)	
Worsening, *n* (%)	0	0	
Hyposmia/anosmia			
Improvement, *n* (%)	0	9 (64%)	0.001
No change, *n* (%)	12 (92%)	5 (36%)	
Worsening, *n* (%)	1 (8%)	0	
Snoring			
Improvement, *n* (%)	2 (15%)	7 (50%)	0.103
No change, *n* (%)	10 (77%)	7 (50%)	
Worsening, *n* (%)	1 (8)	0	
Hedache/facial pain			
Improvement, *n* (%)	1 (8%)	9 (64%)	0.004
No change, *n* (%)	12 (92%)	5 (36%)	
Worsening, *n* (%)	0	0	

Table 3
Changes in endoscopic assessment.

	Hyaluronate (N = 13)	Hyaluronate + tobramycin (N = 14)	P-value
Status of the nasal mucosa			
Improvement, *n* (%)	2 (15%)	11 (79%)	0.002
No change, *n* (%)	11 (85%)	3 (21%)	
Worsening, *n* (%)	0	0	
Mucopurulent secretion of osteomeatal complex			
Reduced, *n* (%)	2 (15%)	11 (79%)	0.002
No change, *n* (%)	10 (77%)	3 (21%)	
Increased, *n* (%)	1 (8%)	0	
Hypertrophy of the right turbinate			
Improvement, *n* (%)	2 (15%)	3 (21%)	1.00
No change, *n* (%)	11 (85%)	11 (79%)	
Worsening, *n* (%)	0	0	
Hypertrophy of the left turbinate			
Improvement, *n* (%)	2 (15%)	4 (29%)	0.55
No change, *n* (%)	10 (77%)	8 (57%)	
Worsening, *n* (%)	1 (8%)	2 (14%)	

The analysis of endoscopic evaluation showed that the combination of HA and Tobramycin was more effective than HA alone in improving the status of the nasal mucosa and in reducing nasal mucopurulent secretions. In contrast, no significant differences between treatments were observed for hypertrophy of the right and left turbinate (Table 3).

More patients in the HA and tobramycin group had negative nasal swab culture for *S. aureus* at the end of treatment compared to patients receiving HA alone (57% vs. 31%), although no statistical significance was detected (P = 0.25). However, the analysis of bacterial load showed a quite similar effect of the two treatments in reducing *S. aureus* in nasal swab culture.

Of note, all the patients with positive nasal swab culture for *P. aeruginosa* had a reduction of bacterial load after HA and tobramycin treatment (Table 4). No patient showed acquisition of *P. aeruginosa* after HA treatment.

To account for the different prevalence of *P. aeruginosa* between the two treatment groups, we performed a further analysis excluding the 4 patients with positive *P. aeruginosa* swab culture. The greater efficacy of the formulation containing HA and tobramycin was confirmed after removing the potential confounding effect of *P. aeruginosa* in sinus. A greater proportion of patients treated with HA and tobramycin experienced a reduction of ENT symptom, compared to patients receiving HA alone [Hyposmia/anosmia 6 (60%) vs. 0, P = 0.02; headache/facial pain 7 (70%) vs. 1 (8%), P = 0.006]. The status of the nasal mucosa improved in 8 patients (80%) receiving HA and tobramycin and in 2 (15%) treated with HA alone, P = 0.003. Similarly, the proportion of patients who had a reduction of mucopurulent secretions of the osteomeatal complex was greater in patients receiving HA and Tobramycin [9 (90%) vs. 2 (15%), P = 0.001].

3.1. Comparison of nasal and sputum culture at baseline

At screening visit, sputum was collected in 55 out of the 59 screened patients. Compared to nasal samples, *P. aeruginosa* was detected in a higher proportion of sputum culture (20% vs. 9%), whereas the proportion of positive cultures for *S. aureus* was similar (60% vs. 65%).

A significant association between infections of the upper and lower airways was observed. The probability of finding a positive sputum culture in patients with a positive nasal specimen was 7.88-fold higher for *P. aeruginosa* and 3.32-fold higher for *S. aureus* compared with patients with a negative nasal culture (Table 5).

4. Discussion

A major therapeutic purpose for patients with CF is to prevent or delay chronic lung infections with CF-pathogenic Gram-negative bacteria. CF-associated chronic rhinosinusitis promote bacterial overgrowth that may represent a gateway for bacterial colonization of the lower airways. This speculation is supported by the findings of Mainz et al. [7], who found the upper and lower airways of CF patients colonized by genotypically identical strains of *S. aureus* and *P. aeruginosa*.

Common bacterial infections can develop in the context of nasal congestion and obstruction and exacerbate the inflammatory reaction. In this perspective, the treatment of the chronic inflammatory processes that characterize rhinosinusitis may prevent spread of infection and inflammation to the lower airways.

HA by inhalation is presently in clinical use in CF in consideration of its water-retaining, re-epithelizing and anti-inflammatory properties as well as of its capacity to restore ciliary beat functions [11,12,15–18]. Moreover, intranasal sodium hyaluronate was well tolerated in patients following functional endoscopic sinus surgery for non CF-nasal polyposis [15].

Table 4
Nasal microbiology at the end of treatment.

		Hyaluronate (N = 13)	Hyaluronate + tobramycin (N = 14)	P-value
Staphylococcus aureus				
Nasal swab	Negative, *n* (%)	4 (31%)	8 (57%)	0.25
	Positive, *n* (%)	9 (69%)	6 (43%)	
	Bacterial load[a]			
	Reduced, *n* (%)	9 (69%)	11 (79%)	0.68
	No change, *n* (%)	2 (15%)	3 (21%)	
	Increased, *n* (%)	2 (15%)	0	
Pseudomonas aeruginosa				
Nasal swab	Negative, *n* (%)	13 (100%)	11 (79%)	0.22
	Positive, *n* (%)	0	3 (21%)	
	Bacterial load[a]			
	Reduced, *n* (%)	0	4 (29%)	0.098
	No change, *n* (%)	13 (100%)	9 (64%)	
	Increased, *n* (%)	0	1 (7%)	

[a] To evaluate the change in bacterial load after treatment, we calculated the differences between baseline and end of treatment of mean bacterial load of right and left nostril.

We therefore carried out a randomized pilot study to evaluate the potential benefits of topic treatment of HA with tobramycin in CF-associated bacterial rhinosinusitis.

We hypothesized that when administered by the nasal spray formulation, HA may be beneficial in alleviating symptoms by covering the nasal mucosa with a softening and protective film, thus providing a protective barrier and preventing dehydration. HA may also facilitate the regeneration and hydration of the mucous layer, thus improving its viscoelasticity and making it easier to eject it adequately; by stimulating ciliary beating binding to receptor for HA-mediated motility (RHAMM) [19], hyaluronan would contribute to the removal from the nasal cavities of mucous deposits and irritant agents, including pathogens. In addition, the bacteriostatic and even the bactericidal effect of tobramycin may be strengthen by the three times a day administration as it was planned in our study.

We enrolled patients with a positive nasal swab for respiratory pathogens: in agreement with previous studies in children and adolescents, *S. aureus* was the predominant microorganism [20], whereas *P. aeruginosa* has been isolated more frequently from the upper airways of adult patients [8]. Endoscopic samples targeting for the sinus ostia were obtained, which have been shown to agree with maxillary sinus cultures [21]. An interesting ancillary observation is that we found a higher probability of lower airways infection by both *S. aureus* and *P. aeruginosa* in patients with a positive sinus specimen. These findings seem to support the results of the study by Mainz et al. [7] who found identical genotypes in upper and lower airways, suggesting that the upper airways play a role as a reservoir of *S. aureus* and *P. aeruginosa* in CF.

Table 5
Association between lower and upper airways infections in screened patients (N = 55[a]).

	Positive sputum cultures	Negative sputum cultures	Total	OR (95% CI)
Pseudomonas aeruginosa				
Positive nasal cultures	3	2	5	7.88 (1.13–54.93)
Negative nasal cultures	8	42	50	
Total	11	44	55	
Staphylococcus aureus				
Positive nasal cultures	23	9	32	3.32 (1.07–10.27)
Negative nasal cultures	10	13	23	
Total	33	22	55	

[a] Sputum collection was not performed in 4 patients.

The nasal spray formulation containing tobramycin and HA was well tolerated and more effective than that containing HA alone, not only in reducing ENT symptoms but also in restoring eutrophism of the nasal mucosa, an effect that has never been demonstrated previously with sodium HA alone. Equally evident is the improvement of "mucopurulent nasal drip," which was observed with the combination of tobramycin-HA, but not with HA solution alone: after 14 days of treatment, no endoscopic traces of mucopurulent secretion were appreciated in the nasal fossae of 86% of patients treated with tobramycin-HA compared with only 15% of patients receiving HA alone.

The therapeutic benefit derived from the association of the two components may be explained by strengthening of the eutrophic action of HA induced by the presence of tobramycin.

The nasal mucosa is colonized by both Gram-positive and Gram-negative bacteria that produce hyaluronidase and facilitate HA degradation, thus reducing its effectiveness. Hyaluronidase cleaves the HA into lower molecular weight fragments which are less effective; tobramycin, by lowering the bacterial load, may delay the enzymatic degradation of HA and consequently prolong its activity, thus playing a crucial role when present in the formulation together with HA. The well-known water-retaining activity of HA may also be enhanced in terms of duration and entity by the bacteriostatic action of tobramycin. Mucosal hydration and restoration of the aqueous layer would promote mucociliary clearance and facilitate the removal of contaminating particles, including bacteria, thus reducing sinonasal inflammation and symptoms.

A significant endoscopic improvement was documented in terms of increased mucosal trophism and reduced secretions. Similarly, with regard to symptoms, although HA alone induced a reduction of ENT symptoms, the addition of tobramycin resulted in a further improvement as a result of the reduction of bacterial load and consequently of secretions in the osteo-meatal complex and in the nasal fossae. Treatment with tobramycin-HA spray increased the thickness and trophism of the nasal epithelium as compared with HA alone treatment. This better trophism of the nasal mucosa may represent repair from epithelial damage caused by chronic sinonasal inflammation.

In contrast, we could not demonstrate that the formulation containing tobramycin and HA was more effective than HA alone in the eradication of *S. aureus* from upper airways and in reducing the bacterial load. The sample size was probably too small for this outcome, and this issue should be further investigated.

The present study suggests that the combination therapy with HA plus tobramycin was more effective than HA alone in the treatment of bacterial rhinosinusitis in CF. The percentage of patients who experienced an improvement of ENT symptoms, a better status of the nasal mucosa and a reduction of mucopurulent secretion at the level of the osteomeatal complex was higher in the group assigned to the combination therapy than in the group that received HA alone.

To our knowledge, this is the first randomized double-blind study that has assessed the tolerability and efficacy of a nasal spray formulation containing HA and tobramycin compared to a control formulation containing HA alone for nasal disease in CF patients. However, a major limitation of our study is that it is not placebo-controlled, and therefore the effects of tobramycin in combination with HA could not be really assessed since HA was administered to both groups.

It should be noted that the prevalence of *P. aeruginosa* infections in our study population is lower than that commonly reported in CF patients. Reducing spread of bacteria in these patients would be a better clinical target. However, we could demonstrate a significant clinical improvement also in patients infected by *S. aureus*.

The efficacy and tolerability of the topical tobramycin-HA treatment in sinonasal disease in CF patients observed in this study should be confirmed in studies on a larger number of patients, particularly those with positive cultures for *P. aeruginosa* and with nasal polyps, in whom such treatment may prove to be even more beneficial.

Authorship

M. Di Cicco and C. Colombo conceived and designed the study. M. Di Cicco and N. Luca performed the ENT examinations. M. Di Cicco and C. Colombo drafted the manuscript. G. Alicandro carried out the data analysis and collaborated with M. Di Cicco, N. Luca, D. Costantini and C. Colombo to data interpretation. L. Cariani and G. Defilippi performed microbiological analysis. L. Claut contributed to data collection. All authors revised the manuscript critically for important intellectual content and approved the final version.

Conflict of interest

None of the authors had a conflict of interest.

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